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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,547	CASTLE ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6-11,13-15 and 23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6-11,13-15 and 23-33* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office action is non-final because new grounds of rejection have been made to claims that were not necessitated by the applicant's amendment.

Claim Objections

2. The objection to claim 25 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim in the Office action mailed 26 March 2004 is withdrawn in view of the amendment to the claim in the amendment filed 01 February 2005.

3. The objection to claims 26-29 in the Office action mailed 26 March 2004 is withdrawn in view of the amendment to the claims in the amendment filed 01 February 2005.

4. The objection to claims 2-10 and 26-29 in the Office action mailed 26 March 2004 is withdrawn in view of the amendment to the claims in the amendment filed 01 February 2005.

5. The objection to claims 11-15 in the Office action mailed 26 March 2004 is withdrawn in view of the amendment to the claims in the amendment filed 01 February 2005.

6. Claim 4 is objected to because of the following informalities: The numeral "6" appears at the end of the claim and it appears to be an extraneous number. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 6 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6 and 31 recite a method of determination of background hybridization level comprising averaging the hybridization signals of the set of genes being analyzed and selecting signals that exceed a pre-selected percentage of the average signal. The specification describes calculation of background signal on page 25, lines 10-13 as follows:

> In a preferred embodiment, background is calculated as the average hybridization signal intensity for the lowest 5% to 10% of the probes in the array, or, where a different background signal is calculated for each target gene, for the lowest 5% to 10% of the probes for each gene.

Because the amendment to claims 6 and 31 filed 01 February 2005 is not supported by the application at the time of filing, a rejection for lack of written description due to new matter is made.

9. The rejection of claims 2-11, 13-15, and 23-29 under 35 U.S.C. 112, second paragraph in the Office action mailed 26 March 2004 is withdrawn in view of the amendment to the claims in the amendment filed 01 February 2005.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 2-4, 6-10, 23, 24, and 26-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4, 6-10, 23, 24, and 26-33 are indefinite for recitation of the phrase "the hybridization signal of each gene in the set of genes to the compound of interest" because genes cannot hybridize to compounds of interest. For the purpose of examination the claims will be assumed to be drawn to expression levels of each gene in the set of genes that are monitored after exposure of the tissue sample to the compound of interest.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al.

The claims are drawn to a method of assessing toxicity of a compound comprising determining the effect of the compound on gene expression and comparing the variability of a composite variable to that of a known toxic compound. In some embodiments the number of genes is greater than 10, a variable is time and dose of the compound, the gene expression data is time stable, contrast analysis, cluster analysis, and principal component analysis is employed, treated liver, kidney, brain, spleen, pancreas, and lung samples are used, the compound is acetaminophen, and factor analysis is used.

Cunningham et al. shows in columns 1-2 a method of comparing the effect of a known toxic compound and a putative toxic compound on gene expression of a treated cell. Microarray polynucleotide hybridization assays are used to assess gene expression. Preferred tissues are listed as liver, kidney, brain, spleen, pancreas, and lung. A preferred toxic compound is acetaminophen. Cunningham et al. shows SEQ ID NOS: 1-61 on column 4 as targets to be assayed for toxic regulation. Cunningham et al. shows clustering of target genes in column 4. As contrast analysis is defined in the specification on page 8 as analysis of genes that are grouped by their response pattern to the toxic compound, Cunningham et al. shows cluster analysis in Tables 1-3 in columns 14-15. Cunningham et al. shows in column 12 that rats were treated for different times with acetaminophen before sacrifice and mRNA isolation. Time variation is a factor analyzed by Cunningham. Time stable is defined in the specification at page 29, lines 17-20, as

changes in gene expression in the same direction for two or more time points. Cunningham shows increases in expression in selected genes for two or more time points in Table 1, column 14. Cunningham et al. does not show use of principal component analysis or variation of dose.

Hilsenbeck et al. show in the abstract and throughout the use of principal component analysis to determine those genes that varied the most between two experiments. Hilsenbeck et al. treated mice with breast cancer cells, and then treated the mice with tamoxifen. The mice were sacrificed at various times and mRNA was isolated and analyzed by use of a polynucleotide microarray to assess changes in gene expression during the experiment (see pages 453-454). Hilsenbeck et al. used principal component analysis to determine which genes were the most varied when comparing different mRNA sample sets. Hilsenbeck et al. concludes on page 458 that "principal component analysis of log-transformed data provides a practical approach to data reduction, visualization, and identification of "significant" outlier genes."

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. by use of principal component analysis to analyze the gene expression data because Hilsenbeck et al. shows that principal component analysis can be used to analyze gene expression data of toxicity experiments to determine those gene sets that are most varied by the treatment. It would have been further obvious to vary dose as well as time of treatment to further determine which genes are affected by a toxic compound.

16. Claims 2, 11,15, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above, and further in view of Holden et al.

The claims are drawn to analysis of the effect of carbon tetrachloride on gene expression.

Holden et al. shows treatment of a hepatoma cell line with carbon tetrachloride, followed by isolation of mRNA and polynucleotide microarray analysis of the effect of carbon tetrachloride on gene expression in the treated cells. Forty genes were found to be affected. Holden et al states that their method will allow for study of mechanisms of carbon tetrachloride toxicity.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-5, 7-9, 11-14, 24, and 25 above by use of carbon tetrachloride as the assayed compound because Holden et al. shows that carbon tetrachloride is a toxic compound that affects gene expression.

17. Claims 2, 10, 26, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above, and further in view of Machens et al.

The claims are drawn to analysis toxic compounds on gene expression that uses logistic regression.

Machens et al. shows that use of logistic regression helps in detection of correlation between a patient's HLA genotype and thymic pathology in myasthenia gravis patients. Details of the statistical analysis are given on page 297.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9,

11, 13, 14, 24-28, 30, and 32 above by use of the logistic regression method of Machens et al. because Machens et al. shows that their method can be used to correlate genetic data and disease state and for the purposes of the statistical analysis the data of Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above is equally applicable to analysis by the method of Machens et al.

18. Claims 2 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above, and further in view of Wikstrom et al.

The claims are drawn to analysis toxic compounds on gene expression that uses least squares analysis.

Wikstrom et al. shows that use of least squares analysis helps in detection of correlation of prognostic factors and ultimate development of prostate cancer. The use of least squares analysis is detailed on page 253.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of correlation of a toxic response to a compound and gene expression of Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above by use of the least squares analysis method of Wikstrom et al. because Wikstrom et al. shows that their method can be used to correlate prognostic factors and disease state and for the purposes of the statistical analysis the data of Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 above is equally applicable to analysis by the method of Wikstrom et al.

Conclusion

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD. can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

John S. Brusca 12 April 2005

John S. Brusca
Primary Examiner
Art Unit 1631

jsb